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Interventions to prevent steroid-induced osteoporosis and osteoporotic fractures in Duchenne muscular dystrophy (Review)

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Interventions to prevent and treat corticosteroid-induced osteoporosis and prevent osteoporotic fractures in Duchenne muscular dystrophy

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ABSTRACT

Background

Corticosteroid treatment is considered the 'gold standard' for Duchenne muscular dystrophy (DMD); however, it is also known to induce osteoporosis and thus increase the risk of vertebral fragility fractures. Good practice in the care of those with DMD requires prevention of these adverse effects. Treatments to increase bone mineral density include bisphosphonates and vitamin D and calcium supplements, and in adolescents with pubertal delay, testosterone. Bone health management is an important part of lifelong care for patients with DMD.

Objectives

To assess the effects of interventions to prevent or treat osteoporosis in children and adults with DMD taking long-term corticosteroids; to assess the effects of these interventions on the frequency of vertebral fragility fractures and long-bone fractures, and on quality of life; and to assess adverse events.

Search methods

On 12 September 2016, we searched the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL Plus to identify potentially eligible trials. We also searched the Web of Science ISI Proceedings (2001 to September 2016) and three clinical trials registries to identify unpublished studies and ongoing trials. We contacted correspondence authors of the included studies in the review to obtain information on unpublished studies or work in progress.

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Selection criteria

We considered for inclusion in the review randomised controlled trials (RCTs) and quasi-RCTs involving any bone health intervention for corticosteroid-induced osteoporosis and fragility fractures in children, adolescents, and adults with a confirmed diagnosis of DMD. The interventions might have included oral and intravenous bisphosphonates, vitamin D supplements, calcium supplements, dietary calcium, testosterone, and weight-bearing activity.

Data collection and analysis

Two review authors independently assessed reports and selected potential studies for inclusion, following standard Cochrane methodology. We contacted study authors to obtain further information for clarification on published work, unpublished studies, and work in progress.

Main results

We identified 18 potential studies, of which two, currently reported only as abstracts, met the inclusion criteria for this review. Too little information was available for us to present full results or adequately assess risk of bias. The participants were children aged five to 15 years with DMD, ambulant and non-ambulant. The interventions were risedronate versus no treatment in one trial (13 participants) and whole-body vibration versus a placebo device in the second (21 participants). Both studies reported improved bone mineral density with the active treatments, with no improvement in the control groups, but the abstracts did not compare treatment and control conditions. All children tolerated whole-body vibration treatment. No study provided information on adverse events. Two studies are ongoing: one investigating whole-body vibration, the other investigating zoledronic acid.

Authors' conclusions

We know of no high-quality evidence from RCTs to guide use of treatments to prevent or treat corticosteroid-induced osteoporosis and reduce the risk of fragility fractures in children and adults with DMD; only limited results from two trials reported in abstracts were available. We await formal trial reports. Findings from two ongoing relevant studies and two trials, for which only abstracts are available, will be important in future updates of this review.

PLAIN LANGUAGE SUMMARY

Treatments to prevent and treat thinning of bones and prevent fractures caused by corticosteroids in Duchenne muscular dystrophy

Review question

What are the effects of treatments to prevent or treat thinning of bones (osteoporosis) and prevent fragile bones from breaking (fragility fractures) in adults and children with Duchenne muscular dystrophy (DMD) who are taking long-term corticosteroids?

Background

DMD is an inherited condition, affecting about one in 3500 to one in 6000 newborn boys. DMD causes muscle weakness that becomes more severe with age. Muscle weakness is widespread, affecting movement, the digestive system, breathing, and the heart. The pattern of weakness mainly affects muscles near the trunk, around the shoulders, and at the hips. If untreated, DMD leads to death in the late teens from breathing or heart complications. A child with DMD often shows the first signs of this disease before starting school. If untreated, he will lose the ability to walk by the age of 13 years and need to use a wheelchair. There is no cure for DMD, but medicines called corticosteroids slow muscle damage and enable boys with DMD to walk for longer. Boys with DMD also tend to have weak bones because of their weak muscles and reduced mobility.

Corticosteroids cause osteoporosis (thinning of the bones), which makes the bones more fragile and liable to fracture (break). Therapies, such as vitamin D and calcium supplements, more calcium in the diet, medicines called bisphosphonates, testosterone, and weight-bearing exercise, might be able to strengthen bone to prevent and treat osteoporosis and prevent fractures in people with DMD who are taking corticosteroids. Investigators use bone density as a measure of how strong the bone is and to measure the effects of therapies to prevent and treat osteoporosis.

Study characteristics

Interventions to prevent and treat corticosteroid-induced osteoporosis and prevent osteoporotic fractures in Duchenne muscular dystrophy (Review)

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We searched the medical literature comprehensively, finding two completed trials. Only brief reports (abstracts) of these trials are available. The participants were children aged from five to 15 years with DMD who were able to walk and not able to walk. The treatments were risedronate versus no treatment in one trial (with 13 participants) and whole-body vibration versus a placebo (inactive) device in the other (with 21 participants).

Key results and quality of the evidence

We found two completed studies that were potentially eligible for this review, for which full results have not yet been published, and two studies ongoing at the time of the search. These studies are looking at the effects of whole-body vibration (two studies), risedronate, and zoledronic acid. Both completed trials, presented as abstracts only, reported an improvement in bone mineral density in children who received active treatment and no improvement in children in the control (placebo or no treatment) groups. However, the reports did not report results for the comparison of treatment versus control groups, which means that it is not possible to draw conclusions about the effectiveness of either treatment. All children tolerated whole-body vibration treatment. Neither study provided information on adverse events.

We know of no evidence from randomised clinical trials to guide use of treatments to prevent or treat osteoporosis and prevent fragility fractures in people with DMD taking corticosteroids.

Searches are current to September 2016.

BACKGROUND

Description of the condition

Duchenne muscular dystrophy (DMD)

Duchenne muscular dystrophy (DMD) is a progressive disorder affecting skeletal, cardiac, and smooth muscle (Emery 1998; Voisin 2004). Inheritance is sex-linked recessive, and the condition has an incidence of one in 3500 to one in 6000 male live births (Emery 1991; Emery 2003; Flanigan 2012). DMD is caused by deletions, duplications or mutations in the dystrophin gene located at Xp21, resulting in the absence or low levels of the protein known as dystrophin (Chaturvedi 2001; Flanigan 2009; Lee 2012; Muntoni 2003; Soltanzadeh 2010). Dystrophin is a large protein located on the sarcolemmal membrane. It forms part of the dystrophin-associated protein complex and is involved in membrane integrity. Absence of dystrophin leads to membrane damage and progressive dystrophic changes within the muscle (Blake 2002; Deconinck 2007). Affected boys appear normal at birth and first show signs of muscle weakness in early childhood, often as a toddler. Without treatment, they become wheelchair dependent by 13 years of age. Without respiratory support, death occurs in the late teens or early twenties. Because of postural imbalance and reduced muscular support to the spine, scoliosis (spinal deformity) typically develops. Scoliosis of the thoracic region restricts movement of the ribs making breathing even more difficult for already weakened

respiratory muscles. However, in recent years, prognosis has improved substantially with the introduction of non-invasive ventilation support along with cough-assist technology and co-ordinated multidisciplinary care (Bushby 2010; Passamano 2012).

Corticosteroid treatment is now considered the 'gold standard' for DMD, and corticosteroid-induced osteoporosis is an important emerging problem (Bushby 2010). Corticosteroids have been shown to slow the decline in muscle function and may protect cardiac and respiratory function. Corticosteroid-treated boys lose the ability to walk at around 12 to 14 years of age, compared with seven to 13 years for non-treated boys (Matthews 2010; Ricotti 2012). Physicians usually start treatment during the 'plateau phase' of the condition (usually between four and six years of age) (Bushby 2010). Doses of prednisone, prednisolone, or deflazacort are either taken daily, Biggar 2004; Fenichel 1991; Griggs 1991; Matthews 2010; Mesa 1991, or intermittently, Dubowitz 2002; Kinali 2002. Treatment that is continued after the loss of ambulation may preserve upper body strength, respiratory and cardiac function, and delay the onset of scoliosis (Balaban 2005; Biggar 2004; Biggar 2006; Daftary 2007; Hussein 2014; King 2007; Lebel 2013; Manzur 2008; Schram 2013). Corticosteroids have significant side-effects, which require proactive management (Angelini 2007; Balaban 2005; Biggar 2006; Bonifati 2000; Bushby 2004; Bushby 2010; Houde 2008; King 2007; Manzur 2008; Matthews 2010; Merlini 2012; Moxley 2010). One such side-effect is corticosteroid-induced osteoporosis, which includes the increased risk of vertebral fractures (Angelini 2012; Bachrach 2005; Balaban 2005; Bothwell 2003; Bianchi 2003; Canalis 2004; Houde 2008; King

2007; Mayo 2012; Quinlivan 2010; Soderpalm 2007; Van Staa 2003; Weldon 2009).

Osteoporosis

Osteoporosis is a progressive, systemic skeletal disease, characterised by reduced bone mass and micro-architectural deterioration of bone tissue. As a result, bone is increasingly fragile and more susceptible to fracture (NICE 2012). Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture. Osteoporotic fragility fractures are defined as fractures associated with low bone mineral density and include spine, forearm, hip, and shoulder fractures.

In children and adolescents, osteoporosis is defined as low bone mineral content or bone mineral density for chronological age. The diagnosis of osteoporosis requires the presence of both a clinically significant fracture history, for example, vertebral compression fracture or long-bone fractures, and low bone mineral content or bone mineral density. Low bone mineral content or bone mineral density is defined as bones with a Z-score that is less than or equal to -2.0, adjusted for age, gender, and body size, as appropriate (ISCD 2007).

Bone mineral content and bone mineral density are assessed in children by dual-energy X-ray absorptiometry (DXA) (Bianchi 2010). Quantitative-computed tomography, peripheral quantitative-computed tomography, quantitative ultrasonography, or magnetic resonance imaging (MRI) are also used (Bachrach 2011; Buckner 2015). To avoid incorrect estimations, conventional DXA measurements are adjusted according to size for use in children, those with deteriorating bone, and people of shorter stature (Bianchi 2014). Bone mineral density is measured as age-based and height-adjusted Z-scores (Bachrach 2011; Baim 2008; Bianchi 2010; Crabtree 2014; Fewtrell 2003). DXA can also predict the risk of fractures before they occur. Its use is based on a relationship between low bone mineral density and risk of fracture in adults, which also exists in children (Clark 2006; Goulding 1998). This is an important application of DXA in patients with DMD, as part of bone health evaluation (Bianchi 2011a).

Bone is a living tissue, which bone formation and bone resorption constantly remodels (Joyce 2012). Factors that affect bone health include genetics, nutrition, physical activity (loading), age, and hormones. Corticosteroid treatment affects endocrine function, suppressing growth, delaying puberty, reducing bone mineral density, and increasing body weight (Bianchi 2011a; Dooley 2013; Wood 2015). Corticosteroids induce bone loss by hindering bone formation through osteoblastic apoptosis (the death of cells that make bone) and by stimulating bone mineral resorption through an increase in the number of osteoclasts (cells that break down bone) (Popp 2006). The reduction in bone mineral density from changes in bone metabolism is not fully understood (Bianchi 2011a). Deficiencies in testosterone (delayed puberty) and growth hormone, or resistance to an insulin-like growth hormone, and

limited mobility with excessive weight gain contribute to a reduction in bone mineral density (Allen 1998; Bianchi 2011a; Dooley 2013). Bone mineral density is difficult to assess in DMD due to lack of normative curves, short stature, delayed bone age, etc. Corticosteroid treatment may not appear to reduce bone mineral density to the same extent as in adults. Soderpalm 2008 commented that lower bone mineral density in boys with DMD is likely to be the combined result of corticosteroid treatment, muscle loss from the disease, and reduced mobility. Low bone mineral density increases the risk of bone fragility fractures (Bachrach 2005; Douville 2005; Joyce 2012; Quinlivan 2005; Talim 2002). There are some data to suggest that boys with DMD who are corticosteroid-naïve (that is, those who have not previously been exposed to corticosteroids) are at increased risk of long-bone fractures (Biggar 2006; Granata 1991; Houde 2008; Hsu 1979; Larson 2000; McDonald 2002; Vestergaard 2001), implying that corticosteroids are not the only cause for these fractures and causation is complex.

Osteoporotic fragility fractures

Vertebral fragility fractures are recognised as the most common manifestation of corticosteroid-induced osteoporosis (Al-Osail 2010; Rodd 2012; Sugiyama 2011; Van Staa 2000; Van Staa 2001; Van Staa 2003; Varonos 1987). Vertebral fragility fractures have not been reported in corticosteroid-naïve patients with DMD of any age (Alman 2004; Houde 2008; King 2007), and very often, vertebral fractures are not tracked in children with DMD (especially those not treated with steroids). In boys with DMD taking corticosteroids, the occurrence of vertebral fractures ranges from 15% to 75% after a mean duration of 6.3 years on treatment (ranging from 4.5 to 8.0 years) (Bothwell 2003; Houde 2008; King 2007; Mayo 2012). The incidence of long-bone fractures was, however, similar in treated and untreated patients (Houde 2008; McDonald 2002) (24% and 26%, respectively, in Houde 2008).

Those treated with corticosteroids tend to be more ambulant, and patients who are more ambulant are more likely to fall and sustain a long-bone fracture. Non-ambulatory patients appear to be at an increased risk of vertebral fractures (Larson 2000; Mayo 2012). Previous surgical intervention for scoliosis may also prevent vertebral fragility fractures (Mayo 2012). Lack of ambulation, taking steroids previously, or both, may lead to a greater body fat composition in patients with DMD. Body fat percentage was reported as significantly higher in patients with vertebral fractures (47.8% \pm 12%) than in those with long-bone fractures (33% \pm 14.2%) (P < 0.05) (Mayo 2012).

Vertebral fractures can be symptomatic or asymptomatic. Acute back pain is closely associated with symptomatic vertebral fragility fractures (odds ratio (OR) 10.6, 95% confidence interval (CI) 2.1 to 53.8, P = 0.004) and requires radiological investigation to confirm the diagnosis (Huber 2010; Talim 2002), but an es-

estimated 20% of vertebral fractures are asymptomatic (Manzur 2010). Asymptomatic fractures are thought to be precursors of painful symptomatic fragility fractures (Leung 2011). Asymptomatic fractures may be undetected because radiological or densitometric monitoring is not conducted routinely (Quinlivan 2010). Diagnosis and confirmation of a vertebral fracture requires visual examination of lateral X-ray or magnetic resonance imaging (MRI) images to assess the change in shape of the vertebrae as biconcave, wedge, or crush, as well as the degree of deformity (Genant 1993; Lenchik 2004; Quinlivan 2010).

The occurrence of fractures is significantly related to low bone mineral density in DMD (Aparicio 2002; Khatri 2008; Larson 2000). Bone mineral density is often lower than normal for the age of the patient (Bianchi 2003; Crabtree 2010; Mayo 2012; Soderpalm 2012). In children and adolescents with DMD, the baseline bone mineral density is low due to lack of weight-bearing activity. It is probably lowered further by corticosteroids. While some studies have shown no reduction in spinal bone mineral density after 30 months of corticosteroid therapy for DMD in prepubertal boys (Crabtree 2010), or only a marginal reduction in children and adolescents taking corticosteroids (Cohran 2008), others reported a substantially lowered bone mineral density in boys (children and adolescents) taking corticosteroids, particularly those with reduced mobility (Bianchi 2003; Hawker 2005; Mayo 2012).

International consensus workshops have taken place to prioritise poor bone health in DMD patients and to improve clinical outcomes through education (Biggar 2005; Leung 2011; Muntoni 2006; Quinlivan 2005; Quinlivan 2010). Recent advances in treatments for muscle loss have enabled people with DMD to actively participate in life for longer. Bone health in patients with DMD is an important issue because long-bone fractures seriously harm mobility: approximately 20% to 50% of independently mobile patients lose the ability to walk unaided following a long-bone fracture (Larson 2000; Manzur 2010; Mayo 2012; McDonald 2002; Vestergaard 2001). Identifying treatment strategies to prevent corticosteroid-induced osteoporosis and prevent often painful fragility fractures in DMD may have a significant effect in improving quality of life for these patients.

Description of the intervention

The following pharmacological and non-pharmacological interventions are thought to have the potential to prevent or treat corticosteroid-induced osteoporosis by increasing bone mineral density and reduce the risk of fractures in patients with DMD.

Bisphosphonates

Intravenous bisphosphonates are used to treat painful vertebral fractures in boys with DMD and are associated with improvements in back pain (Sbrocchi 2012). The use of bisphosphonate

treatment in children is relatively new, but there are growing numbers of trials suggesting benefit, particularly in children with osteogenesis imperfecta (bone fragility) (Allington 2005; Bianchi 2000; Brumsen 1997; Glorieux 1998; Hawker 2005; Henderson 2002; Houston 2014; Palomo 2011; Plotkin 2000; Plotkin 2006; Rauch 2002; Rudge 2005; Sbrocchi 2012; Shaw 2000; Sholas 2005; Wagner 2011; Ward 2011). A randomised controlled trial (RCT) to investigate the efficacy and safety of daily oral alendronate in children and adolescents with osteogenesis imperfecta over two years found that the mean spine area Z-score increased from -4.6 to -3.3 compared to -4.6 to -4.5 in the placebo group. Long-bone fracture incidence and bone pain were similar between groups (Ward 2011).

Bisphosphonates appear to be well tolerated by children for periods of up to three years (Shaw 2005; Ward 2007b). Dosing regimes differ among paediatric studies (Ward 2007b). Oral bisphosphonates are prescribed according to body weight (mg/kg) (Bianchi 2000; Hawker 2005; Rudge 2005). Intravenous bisphosphonates are usually administered at a dose of 1 mg/kg to 1.5 mg/kg (Acott 2005; Shaw 2000).

Treatment is usually combined with vitamin D and calcium supplements to minimise the risk of hypocalcaemia (Maalouf 2006; Poole 2012); however, calcium supplements reduce the absorption of bisphosphonates. Adverse effects are more common with intravenous than oral bisphosphonates (Somalo 2007). The U.S. Food and Drug Administration (FDA) is reviewing long-term use (FDA 2011). Atypical fractures occurring with prolonged bisphosphonate therapy have been a featured concern in recent publications (Compston 2011; Edwards 2010; Girgis 2010; Isaacs 2010; Shane 2010), and there have been cautions that high and prolonged doses may paradoxically induce osteoporosis (Whyte 2008).

Calcium

A balanced calcium-rich diet is recommended as the best long-term strategy to maintain adequate calcium levels (Bacciottini 2004; Biggar 2005; Sunycz 2008). Calcium supplements in healthy children have shown short-term improvements in bone mineral density (Winzenberg 2006). Intestinal calcium absorption is dependent on other factors such as vitamin D levels.

Genetics determine 60% to 80% of attained peak bone mass, and environmental factors, such as nutrition, exercise, and disease, determine the remainder (Quinlivan 2010). Bone mineral density can vary between individuals from early childhood and be predictive of a potential fracture risk in children with medical conditions affecting bone health (Ferrari 1998; Goulding 2005; Harvey 2012; Quinlivan 2010; Winzenberg 2006). A review of calcium supplementation for improving bone mineral density in children showed no effect on spinal bone mineral density, but a small effect on total body bone mineral content (BMC) (Winzenberg 2006). A double-blind, placebo-controlled study of 149 girls showed an increase in bone mineral density in those taking calcium-supplemented food

compared to those who did not (Bonjour 1997). There is poor evidence to indicate whether calcium supplementation alone reduces the risk of fractures (Black 2002; Bolland 2015; Goulding 1998; Goulding 2004; Petridou 1997; Winzenberg 2006). The consumption of adequate dietary calcium and vitamin D can increase bone mineral density in patients with DMD (Bianchi 2011). Evidence that calcium alone has a positive effect on bone health in boys with DMD is limited.

Vitamin D

Significantly lower serum 25OHD levels have been highlighted in boys with DMD, especially in those taking corticosteroids (Bianchi 2003; Bianchi 2011). People taking corticosteroids are twice as likely to have low 25OHD levels as those not on corticosteroids (OR 2.36, 95% CI 1.25 to 4.45) (Skversky 2011). Dhawan 2010 proposed that corticosteroids may inactivate 25OHD by increasing the activity of the enzyme 24-hydroxylase.

Vitamin D levels collected in boys with DMD aged from 1.5 to 15.5 years prior to starting corticosteroid treatment revealed that 78% had inadequate levels and 15% qualified as deficient (Munot 2010). In two other studies, 54% to 70% of those with DMD on corticosteroids were vitamin D deficient (Manzur 2010; Wong 2010).

In a Cochrane Review, the bone mineral density in healthy children taking vitamin D supplements did not change, but bone mineral density did increase in those with low 25OHD levels (Winzenberg 2010). When investigators examined vitamin D levels at the time of a vertebral fracture in boys with DMD, they categorised the mean serum vitamin D levels as insufficient (Manzur 2010).

Testosterone

Testosterone is the primary sex hormone for the maturation of sex characteristics in adolescent males. It is also involved in the increase in muscle strength and bone mineral content during puberty (Seeman 2001; Wood 2015). Testosterone is a steroid hormone produced by the testes and the adrenal glands and belongs to a group of male hormones known as androgens. The production of this hormone is regulated by the hypothalamus and pituitary gland.

Long-term corticosteroid treatment in prepubertal boys can slow down growth and delay puberty compared to their healthy peers (Wood 2015). All but one of 44 boys with DMD aged 13 years and upwards assessed at Cincinnati Children's Hospital were prepubertal, compared to the 50% of healthy UK boys who are in puberty by 12 years of age (Bianchi 2011a; Bonifati 2000). Although not clearly understood, high doses of corticosteroids inhibit or reduce the secretion of gonadotrophin-releasing hormone by the hypothalamus, which in turn down-regulates pituitary gonadotrophin production. Corticosteroids may also have a direct effect on the testes to reduce testosterone production. A deficiency

in testosterone can delay the onset of puberty (Al-Harbi 2008; Eastell 1998; Hampson 2002; Kamischke 1998a; Reid 1985).

The absence or delay of puberty has a significant adverse effect on bone health, which is already poor in those with DMD due to corticosteroid treatment, diminishing muscle mass, and reduced mobility (Bianchi 2011a; Fairfield 2001; Guzman 2012; Reid 1985). Hypogonadism increases the risk of osteoporosis and fractures. Testosterone is an important hormone involved in the development of bone and in the maintenance of bone mineral density in adolescence and adulthood (Amory 2004; Devogelaer 1992; Katznelson 1996; Kenny 2001; Leder 2002; Tenover 1992).

Weight-bearing exercise

In DMD patients over eight years of age, there is a gradual decline in physical activity due to natural disease progression (Mazzone 2011; McDonald 2010). Weight-bearing exercise, for example, walking, stimulates bone regeneration. Dynamic-loading activity achieves greater gains in bone tissue than static activity (Lanyon 1984). Muscle weakness hinders dynamic weight-bearing exercise and has a negative impact on bone development. Disuse of the skeleton as a result of prolonged inactivity degenerates bone tissue further.

How the intervention might work

In children with corticosteroid-induced osteoporosis, the rate of bone resorption exceeds that of bone formation. The main focus of interventions is either to slow bone resorption or promote bone formation to increase bone mineral density whilst receiving corticosteroid therapy. These interventions can be used alone or in combination to prevent or treat bone loss.

Bisphosphonates

Bisphosphonates are drugs that inhibit bone resorption by causing apoptosis of osteoclasts (Fleisch 2003; Poole 2012; Rogers 2011; Russell 2008). They are inorganic analogues of naturally occurring pyrophosphates, which prevent calcification by binding to hydroxyapatite salt in bone (Nancollas 2006; Russell 2011; Sebestyen 2012). Bisphosphonates accumulate at bone resorption sites in the skeleton and stop osteoclast-mediated activity (Dominguez 2011; Drake 2008; Fleisch 2003; Hughes 1989; Hughes 1995; Sato 1991; Sebestyen 2012; Somalo 2007). There are two groups of bisphosphonates: non-nitrogen-containing bisphosphonates (etidronate, clodronate, and tiludronate) and nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronate). The presence of a nitrogen or amino group in the chemical structure of bisphosphonates increases the potency of the drugs for osteoclastic activity (Drake 2008; Ebetino 2011; Reszka 2004). These more potent nitrogen-containing bisphosphonates are often used to treat

children with corticosteroid-induced osteoporosis and osteopenia (Allington 2005; Black 2012; Brumsen 1997; Hawker 2005; Poole 2012; Rudge 2005; Schwartz 2010; Sholas 2005).

Calcium

Calcium is essential to enable normal bone growth and development in children and adolescents (Flynn 2003; Peacock 2010). When combined with phosphate, calcium has a structural role in bone health as a component of bone matrix hydroxyapatite, which provides compressional strength in bone (Bonjour 2011; Peacock 2010). During remodelling, bone turns over calcium. Remodelling activity determines the amount of calcium required to maintain bone health, and this varies throughout life (Mesias 2011). Calcium requirements are greater during adolescence as growth peaks, and approximately 40% of total skeletal bone mass is acquired (Flynn 2003; Greer 2006; Mesias 2011; Weaver 2006). Calcium deficiency can contribute to the development of osteoporosis. Not only is there inadequate calcium for bone mineralisation, but bone calcium stores are depleted to maintain blood calcium levels. Reduced blood calcium levels triggers parathyroid hormone (PTH) release (Peacock 2010). PTH stimulates osteoclasts and bone resorption. High blood calcium levels result in calcitonin release, which inhibits osteoclast activity, promoting bone formation and storage of excess calcium in the bone matrix.

The relationship between calcium intake and bone mass is complicated in DMD patients because corticosteroid treatment induces bone resorption, transferring calcium from bone to blood. High blood calcium levels prevent further intestinal calcium absorption to build bone. However, adequate calcium intake could slow bone resorption and contribute to improving bone health in boys and adolescents with DMD (Bianchi 2011; Quinlivan 2010). Many intervention studies in DMD patients have advised a daily calcium supplement of 750 mg (Hawker 2005; Mayo 2012).

Vitamin D

Vitamin D is vital for intestinal calcium absorption (Frolik 1971; Wei 2010). It may also have its own protective effect on bone

(Bartoszewska 2010; Peppone 2010). Vitamin D₂ (ergocalciferol) is largely man-made and present in supplemented food. The

skin synthesises vitamin D₃ (cholecalciferol) after exposure to sunlight, and it is also available in the diet (Misra 2008). The liver metabolises vitamin D into calcifediol (25-dihydroxyvitamin

D₃ (25OHD)), which the kidneys convert to the active calcitriol

(1,25-dihydroxyvitamin D₃) (Peppone 2010). Vitamin D deficiency can cause rickets in children and osteomalacia in adults from poor bone mineralisation (Holick 2007; Pela 2012; Misra 2008; Wagner 2008; Ward 2007a). To a lesser extent, vitamin D deficiency contributes to bone resorption and osteoporosis (Joyce

2012; Lips 2006). Many children and young adults in the UK have vitamin D insufficiency from increased use of sunscreens and reduced outdoor activities (Biggar 2005; Davies 2011; Lips 2012; Misra 2008; Pela 2012). Its prevalence, especially in non-white families, is underappreciated (Ahmed 2011; Kehler 2013; Lips 2010; Shaw 2011; Zipitis 2006).

Calcitriol slows bone resorption and enhances bone mineralisation because it aids calcium absorption. Calcitriol influences the genes that control neuromuscular cell proliferation, differentiation, and apoptosis (Banerjee 2003; Carlberg 2003; Garcia 2011). There is little evidence that increasing vitamin D intake alone reduces the risk of fractures (Bischoff-Ferrari 2005; DIPART 2010; Looker 2008).

Testosterone

Testosterone therapy increases trabecular bone density (Katznelson 1996). Testosterone is used to reverse delayed puberty, reduced growth, and osteoporosis exacerbated by corticosteroid use in DMD (Bianchi 2011a).

Testosterone replacement therapy is started in low doses at around 14 years of age and increased over three to four years until adult levels are reached. The expected benefits include an increase in bone density, muscle strength, and energy levels from a pubertal growth spurt.

Testosterone supplementation can also increase height and improve quality of life during adolescence and young adulthood from an improved body image (Landon 1984; Mason 2011). A meta-analysis of eight RCTs examining the use of testosterone in 365 men found moderate gains in lumbar bone density (Tracz 2006). Three of the eight studies included men taking corticosteroids (N = 87). The meta-analysis concluded that the effect of testosterone was weak with regard to osteoporosis prevention and treatment in men, as no bone fracture data were available. Another review of RCTs for the effects of testosterone on body composition in middle-aged men found that testosterone improved bone mineral density at the lumbar spine by 3.7% (CI 1.0% to 6.4%) compared to placebo (Isidori 2005).

Weight-bearing exercise

The most evident decline in vertebral bone mineral density in DMD appears to occur with the loss of independent ambulation, regardless of whether or not the patient is taking corticosteroids (Biggar 2004; Crabtree 2010; Mayo 2012). A reduction in mechanical loading reduces osteoblast bone formation and promotes osteoclast-mediated bone resorption (Takata 2001). A study revealed that bone mineral density at a number of sites including the lumbar spine improved with calcium and exercise in prepubertal and early pubertal boys (Bass 2007; Iuliano-Burns 2003; Stear 2003). The Iowa Bone Development Study found significant longitudinal associations between physical activity that increased

the mechanical loading of the skeleton in boys aged five years and bone mineral content of the hip at eight and 11 years of age (Janz 2010). Growing bone adapts to withstand mechanical loading. In boys with DMD, standing programs and prolongation of walking using mechanical walking aids are common components of management (Pedlow 2015), and boys have shown improvement in vertebral bone mineral density and function capacity (Bianchi 2013; Spencer 1962). More recently, high-frequency, low-intensity whole-body vibration appeared to improve bone health in children and adolescents with a disability (Matute-Llorente 2015; Reyes 2011; Ruck 2010), but was inconclusive in people with DMD (Söderpalm 2013). Regular low-intensity and appropriate exercise strengthens bone tissue, as well as improving the balance of action between opposing muscle groups and balance while standing and moving (Bushby 2010; Grange 2007; Jansen 2010). These interventions could reduce the risk of fractures in non-ambulant boys (Ward 2004).

Why it is important to do this review

Corticosteroids delay the loss of ambulation and cardiorespiratory failure in patients with DMD. However, boys require treatment for many years, and the risk of vertebral fragility and possibly long-bone fractures is high. Identifying treatment strategies to prevent and treat osteoporosis and prevent fragility fractures will improve the quality of life for these patients.

OBJECTIVES

To assess the effects of interventions to delay or treat osteoporosis in children and adults with DMD taking long-term corticosteroids; to assess the effects of these interventions on the frequency of vertebral fragility fractures and long-bone fractures, and on quality of life; and to assess adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for all randomised controlled trials (RCTs) and quasi-RCTs involving treatment or prevention of corticosteroid-induced osteoporosis and prevention of fragility fractures in patients with DMD who were taking corticosteroids. Quasi-RCTs employ methods of allocation that are not truly randomised (for example, by alternation or using date of birth or hospital number).

Types of participants

We considered for inclusion in the review all children, adolescents, and adults with a diagnosis of DMD, with any pathogenic mutation, deletion, or duplication confirmed by genetic testing or muscle biopsy showing the complete absence of dystrophin.

Types of interventions

We considered for inclusion in the review any intervention to prevent or treat corticosteroid-induced osteoporosis or prevent fragility fractures in patients with DMD compared with placebo, another intervention, or no treatment (no available standard care). The interventions included oral and intravenous bisphosphonates (including both non-amino and amino groups), vitamin D supplements, calcium supplements, dietary calcium, testosterone, and weight-bearing activity.

We planned to analyse oral and intravenous bisphosphonates separately.

Types of outcome measures

Primary outcomes

1. Change in vertebral bone mineral density measured by dual-energy X-ray absorptiometry (DXA) and expressed as a Z-score (which is based on age-matched results with a correction for body height) between baseline and 24 months of intervention. The presence of vertebral compression fractures could artificially increase bone mineral density and produce higher Z-scores in an individual. However, we considered this effect unlikely to influence the outcome of a meta-analysis.

Secondary outcomes

Secondary outcomes measured between baseline and 24 months of intervention.

1. The number of vertebral fragility fractures, defined as one or a combination of the following: end-plate deformity with a reduction in the mid-vertebral height (biconcavity), decrease in the anterior vertebral height (wedging), or reduction in the anterior and posterior vertebral height (compression or crush). Identification of such vertebral fractures was based on visual evaluation with an assessment of grade or severity linked to vertebral height, shape, and appearance (Baim 2008), for example, using the Genant visual semi-quantitative method (Genant 1993). Fractures were detected using lateral spinal X-ray, DXA vertebral fracture assessment (VFA), computed-tomography (CT) scans, or magnetic resonance imaging (MRI).
2. The number of long-bone fractures.
3. Change in reported bone pain measured using a standardised pain score (McGrath 2008), such as the visual analogue scale (VAS) (Scott 1979; Zebracki 2008).

4. Change in quality of life, measured using a validated rating scale, for example, the Pediatric Quality of Life Inventory (PedsQL) (Varni 2001), Neuromuscular Module and Generic Core Scales (Davis 2010).

5. Any adverse events; adverse events that led to the withdrawal of treatment; serious adverse events that are fatal, life-threatening, or led to prolonged hospitalisation; and specific adverse events, such as jaw osteonecrosis and atypical femur fractures.

Search methods for identification of studies

Electronic searches

On 12 September 2016, we searched the following databases to identify potentially eligible trials:

- the Cochrane Neuromuscular Specialised Register;
- CENTRAL (the Cochrane Central Register of Controlled Trials) in the Cochrane Register of Studies Online;
- MEDLINE OvidSP (1966 to September 2016);
- Embase OvidSP (1980 to September 2016);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus (1982 to September 2016); and
- Web of Science Core Collection (Proceedings paper or Meeting abstract) (2001 to September 2016).

We did not limit our search by language or publication status. The detailed search strategies are in the appendices.

- Cochrane Neuromuscular Specialised Register (Appendix 1)
- CENTRAL (Appendix 2)
- MEDLINE (Appendix 3)
- Embase (Appendix 4)
- CINAHL Plus (Appendix 5)
- WOS (Appendix 6)

Searching other resources

In addition, we searched the following registries to identify unpublished data, unpublished studies, and ongoing trials:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 11 October 2011);
- the World Health Organization International Clinical Trials Registry Platform (ICTRP, apps.who.int/trialsearch; searched 11 October 2011); and
- the ISRCTN registry (www.isrctn.com; searched 11 October 2011).

We presented detailed search strategies in the appendices.

- ClinicalTrials.gov (Appendix 7)
- ICTRP (Appendix 8)
- ISRCTN registry (Appendix 9)

Data collection and analysis

Selection of studies

Two review authors (JMB and MS) independently reviewed titles and abstracts from the electronic search results and selected papers for full-text review according to the inclusion criteria. We obtained the full text of all potentially relevant studies for further assessment and selected studies that met the inclusion criteria. We would have resolved disagreements by discussion, but there were no disagreements. We agreed by discussion to contact five study authors to obtain further information for clarification on published work, unpublished studies, and work in progress.

We collated multiple reports of the same study under the same study ID. We completed a PRISMA flow diagram, 'Characteristics of excluded studies' tables, and 'Characteristics of ongoing studies' tables to detail the selection process.

A lack of randomised trials, other than two abstracts, meant that the two review authors (JMB and MS) were unable to extract data.

Assessment of risk of bias in included studies

Two review authors (JMB and MS) independently assessed the risk of bias in the included studies, and a third (BB) verified the assessments. We used the domain-based evaluation described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The domains included the following:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessors;
5. incomplete outcome data;
6. selective reporting; and
7. other bias.

For each domain, we graded the risk of bias as high, low, or unclear (Higgins 2011a). We contacted the trial's corresponding authors for clarification of insufficient detail in study reports. We resolved disagreements through discussion with the other review authors, and we assigned studies to the following categories.

- Low risk of bias: all domains at low risk of bias.
- High risk of bias: two or more domains at high risk of bias.
- Unclear risk of bias: one or more domains at unclear risk of bias.

We constructed a 'Risk of bias' table using RevMan to present the results. When considering treatment effects, we planned to take into account the risk of bias in the studies that contributed to the outcome.

We would have used the 'Risk of bias' assessments to perform sensitivity analyses, if sufficient data had been available.

Information on risk of bias related to unpublished data or correspondence with a trialist was noted in the 'Risk of bias' table.

Assesment of bias in conducting the systematic review

We conducted the review according to the published protocol (Bell 2014). We would have reported any deviations from protocol in [Differences between protocol and review](#).

[Appendix 10](#) details methods described in the protocol to be followed if data become available for analysis in future.

Data synthesis

In the absence of meta-analysis or full-text trial reports, we presented the limited data available narratively, in the [Results](#) section.

R E S U L T S

Description of studies

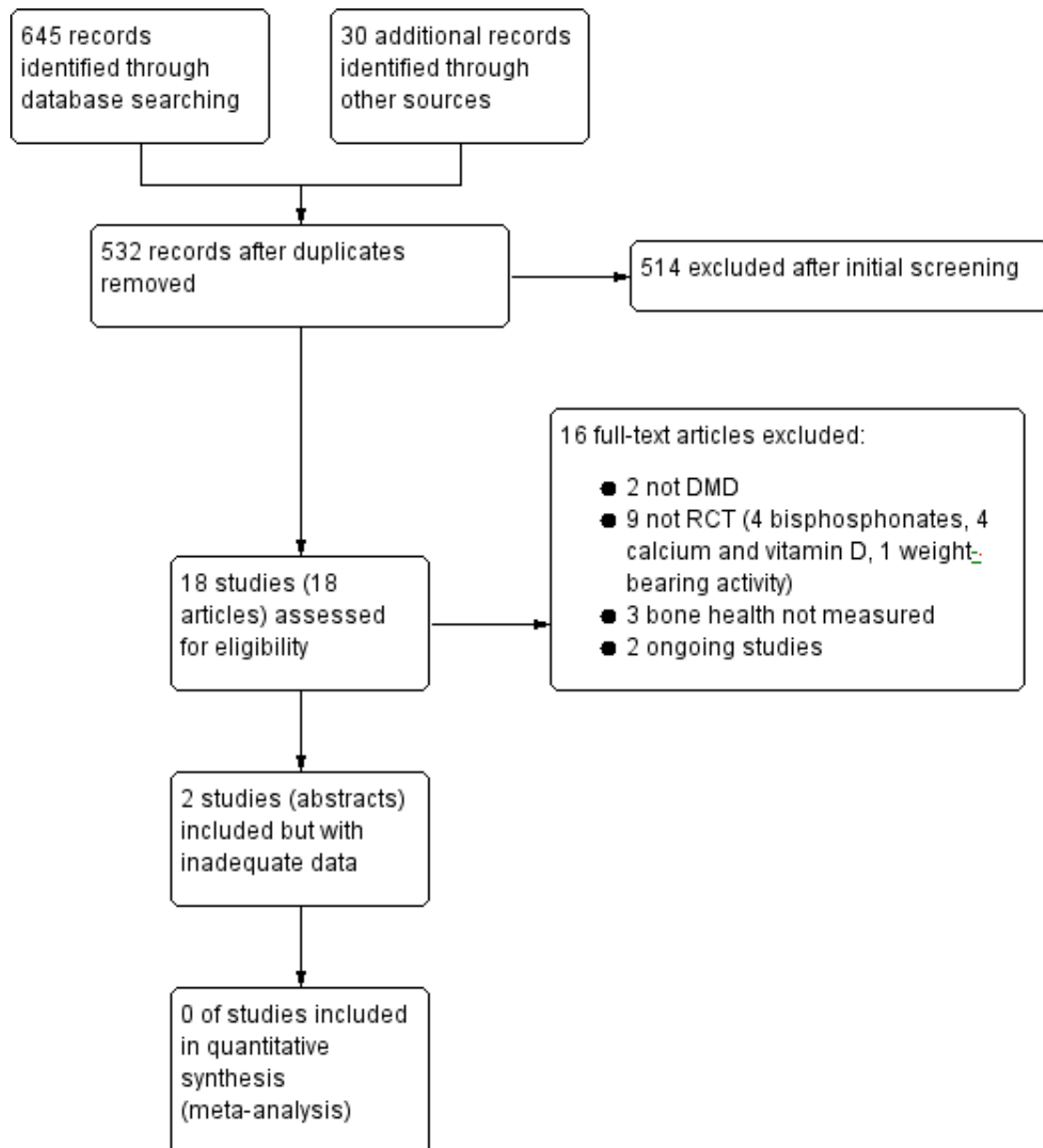
Results of the search

The total number of potentially relevant references retrieved from each database was 645: 58 from the Cochrane Neuromuscular Specialised Register, 78 from the Cochrane Central Register of Controlled Trials (CENTRAL), 303 from MEDLINE, 159 from Embase, 22 from CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus, and 25 from Web of Science ISI Proceedings. The number of references from database searches after deduplication was 506.

We identified 30 additional references from other sources: four from the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov), seven from the IS-RCTN registry, 17 from ICTRP, one published study from correspondence with a co-author (AH), and one unpublished study from correspondence with an author of related studies. The number of studies from these sources after deduplication was 26.

The number of references selected for further review based on their titles and abstracts was 18. Of these, only two met the inclusion criteria for the review, but only conference abstracts were available. We requested unpublished data from the authors of both studies; one responded with further information, and the second did not respond. We categorised two further studies as [Ongoing studies](#). We illustrated the overall study selection process in a flow diagram ([Figure 1](#)).

Figure 1. A flow diagram illustrating the study selection process.



Included studies

We found two randomised clinical trials that appeared relevant for inclusion in this review (see [Characteristics of included studies](#)).

[McSweeney 2014](#) assessed the effects of bisphosphonate therapy (risedronate 1 mg/kg, maximum 35 mg) combined with calcium (500 mg/day) and vitamin D (10 mg/day) compared to calcium and vitamin D alone in a randomised controlled trial (RCT) involving 13 boys with Duchenne muscular dystrophy (DMD). The median age of participants was 8.5 years (range 5.4 to 15.5 years); nine boys were ambulant and on corticosteroid therapy. The abstract did not provide information on funding sources.

[Bianchi 2013](#) investigated weight-bearing activity (low-magnitude high-frequency vibration) compared to the effects of a placebo device on bone mineral density in 21 ambulant boys who had received corticosteroids for at least six months. The trial had a prospective, double-blind, randomised, placebo-controlled design. The abstract did not provide information on funding sources. Both studies were reported in conference abstracts, but there was insufficient information available to collect outcome data or assess risk of bias. We contacted both primary authors for further information: [Bianchi 2013](#) had no further information to offer until publication, and we received no response from [McSweeney 2014](#). We do not have information on when we can expect full publication of the results.

Excluded studies

We excluded 14 studies that did not meet the inclusion criteria for this review (see [Characteristics of excluded studies](#)). The rea-

sons for rejection were that the studies did not include patients with DMD in the study population ([Adachi 2001](#); [Cohran 2013](#)), were not randomised ([Bianchi 2011](#); [Biggar 2004](#); [Cohran 2008](#), [Hawker 2005](#); [Houston 2014](#); [Mayo 2012](#); [Srinivasan 2016](#); [Sbrocchi 2012](#); [Söderpalm 2013](#)), or did not assess the effects of the intervention on bone health ([Dubowitz 1984](#); [Scott 1981](#); [Yilmaz 2004](#)).

Ongoing studies

We found two ongoing clinical studies (see [Characteristics of ongoing studies](#)). The first was a RCT to assess the effect of a novel whole-body vibration therapy on bone health as well as muscle strength ([NCT01954940](#)). This trial was registered on 13 September 2013, with an estimated recruitment end date in March 2015. The study is still recruiting participants (last verified 26 July 2016). The second was a RCT of zoledronic acid (Aclasta) versus vitamin D plus calcium in children and adolescents with DMD, to assess change in lumbar spine bone density over 12 months ([ACTRN12610000507088](#)). The trial was registered on 18 June 2010, and the anticipated date of the enrollment of the last participant is 31 December 2016.

Risk of bias in included studies

See [Characteristics of included studies](#) and [Figure 1](#) and [Figure 2](#) for 'Risk of bias' assessments. As information was only available from abstracts, we were limited in our ability to fully assess risk of bias. We assessed random sequence generation as low risk for both studies ([Bianchi 2013](#); [McSweeney 2014](#)) and blinding as low risk for ([Bianchi 2013](#)). We assessed all other domains as unclear.

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study. Green = low risk of bias; yellow = unclear risk of bias; red (not shown) = high risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bianchi 2013	+	?	+	+	?	?	?
McSweeney 2014	+	?	?	?	?	?	?

Effects of interventions

Risedronate, calcium, and vitamin D versus calcium and vitamin D alone

Studied in [McSweeney 2014](#)

[McSweeney 2014](#) (N = 13) randomised participants with a spine Z-score less than -1.0 to risedronate plus calcium and vitamin D (N = 6) or to calcium and vitamin D alone (N = 7). At baseline and 12 months, investigators measured the spine and whole body bone mineral density Z-score in both groups ([Table 1](#)). The study authors reported a significant improvement in bone mineral den-

sity of the spine and whole body at 12 months compared to baseline in the risedronate group. The published abstract reported no information on fractures. Nine participants were ambulant and taking corticosteroid therapy, but it is unclear whether those taking risedronate were ambulant. If current practice was applied, all participants given risedronate would be taking corticosteroids. The abstract did not provide information on adverse events.

Weight-bearing activity (low-magnitude high-frequency vibration) versus placebo device

Studied in [Bianchi 2013](#)

[Bianchi 2013](#) examined the benefits of low-magnitude high-frequency vibration by randomising 21 ambulant children with DMD taking corticosteroids (mean age 9.3 ± 3.9 years) to either vibration devices ($N = 11$) or placebo devices ($N = 10$). Spine, hip, and whole-body bone mineral density measurements were taken at baseline, six, and 12 months to monitor change in each treatment group. Bone mineral density significantly increased at 12 months versus baseline in the active group only (spine bone mineral apparent density (BMAD): +7.9%, $P < 0.02$; total body (TB): +6.8%, $P < 0.02$; femoral neck: +9.8%, $P < 0.01$). There was “no change or a decrease” in bone mineral density versus baseline in the placebo group (spine BMAD: -2.9%; TB: -3.9%; femoral neck: -4.8%). All children tolerated whole-body vibration treatment. The abstract provided no information on fractures.

DISCUSSION

Summary of main results

This review was only able to include two randomised studies involving a total of 34 boys with Duchenne muscular dystrophy (DMD) ([Bianchi 2013](#); [McSweeney 2014](#)). One study compared risedronate plus calcium and vitamin D with calcium and vitamin D alone; the other compared the effects of whole-body vibration with a placebo intervention. Neither study was published except in abstract form. Although each trial reported improvements in bone mineral density with active treatment over baseline, the abstracts provide insufficient data for analysis or to assess the quality of the evidence.

Evidence from non-randomised studies

In the absence of data from studies meeting the inclusion criteria for this review, we detailed results of non-randomised studies to inform future trial design and provide a platform for new RCTs of needed interventions to improve or stabilise bone health in DMD.

Bisphosphonates

No RCTs of alendronate in boys with DMD have been conducted. A small retrospective study assessed the effects of alendronate in 29 participants with DMD with a mean age of 12 years (23/29 participants had been treated with corticosteroids) ([Houston 2014](#)). Nineteen boys had dual-energy X-ray absorptiometry (DXA) measurements taken during alendronate treatment over a mean of 3.7 years. This study reported a non-significant effect in favour of alendronate on lumbar spine bone mineral density Z-score ([Houston 2014](#)). The lumbar spine bone mineral density Z-score increased from -2.09 to -1.65 ($P = 0.38$). In comparison, seven participants

not taking alendronate but taking corticosteroids only also showed an increase in the mean lumbar spine Z-score (from -1.71 to -1.44 ($P = 0.30$)). This increase could have been caused artificially by scoliosis. In another study, 16 boys taking alendronate over two years maintained a mean lumbar spine Z-score of less than -1 ([Hawker 2005](#)). Each boy was taking deflazacort and bone protection (calcium and vitamin D supplements). Improvements in spinal Z-scores were significantly associated with starting bisphosphonates at a younger age ($P = 0.01$). In both of the above studies a mild gastrointestinal side-effect was the major complaint associated with alendronate.

A retrospective study examined 52 children with DMD taking oral risedronate treatment (treated) for a mean duration of 3.6 years while taking long-term corticosteroids ([Srinivasan 2016](#)). The investigators also collected data from a historical comparison group of children with DMD who took corticosteroids alone ($N = 15$). Risedronate-treated children also received vitamin D supplementation of 800 IU/day to 1000 IU/day; it is not clear if the untreated children also received vitamin D. Risedronate was stopped in 9/52 children due to side-effects (abdominal pain, vomiting, constipation, joint pain, flu-like symptoms, and dizziness). DXA results were available in 35 children who continued risedronate treatment for over 12 months. The treated group DXA scores remained stable (mean 0.04 (standard deviation (SD) 1.3) at baseline and -0.04 (1.2) at final assessment, mean follow-up: 4.9 years). The untreated group mean (SD)-adjusted Z-score decreased from -0.1 (1.3) to -1.00 (1.3) (mean follow-up: 6.2 years). During this study, three ‘treated’ children, all with baseline Z-scores of less than -1 developed lumbar vertebral fractures. This study did not assess the presence of asymptomatic vertebral fractures. Given that it was not clear if the untreated group received vitamin D, it is unclear whether or not the improvement in bone mineral density was due to risedronate or vitamin D or a combination of both. Although no child experienced osteonecrosis of the jaw, a significant proportion of participants stopped taking risedronate because of side-effects.

[Sbrocchi 2012](#) retrospectively studied intravenous bisphosphonate (pamidronate or zoledronic acid) treatment for painful vertebral fractures in boys with DMD. At baseline, there were 27 vertebral fractures among the seven boys. After two years of bisphosphonate treatment, 17 of the fractures showed an improved vertebral height ratio, 10 vertebrae were stabilised, and no vertebrae showed a reduced vertebral height ratio. Treatment did not prevent the development of new vertebral fractures in some participants, but it did remove the associated back pain completely in three boys and improved back pain in the remaining four. The median change in lumbar spine bone mineral density Z-score was 0.5 SD (interquartile range: -0.3 to 1.7). Side-effects occurred mostly with the first dose of intravenous bisphosphonate treatment.

From the non-randomised studies available, bisphosphonate treatment may stabilise bone mineral density. It is not clear if bisphosphonates prevent fragility fractures from the data available. The

effect of bisphosphonates may well depend upon the time they are started in relation to bone fragility appearing.

Vitamin D and calcium

A prospective study in DMD involving 33 participants taking corticosteroids for three years reported that 67% (22 of 33) had an increase in bone mineral density in response to vitamin D (calcifediol and 25-dihydroxyvitamin D₃ (25OHD)) and increased dietary calcium (Bianchi 2011). During the first year of the study, participants had increased dietary calcium but no additional vitamin D, and the bone mineral density decreased at the lumbar spine in all participants, with measured urinary calcium and serum 25OHD levels below normal. In 20 participants, serum 25OHD levels were below 20 ng/ml. During the following years, participants took calcifediol (0.8 mcg/kg/day) and increased dietary calcium (11,236 mg/day, $P < 0.001$). The bone mineral density at the spine significantly increased in 22 participants, urinary calcium increased to normal levels, and serum calcium and 25OHD returned to normal levels. No vertebral fractures occurred during the three-year study, but seven fractures of the leg and foot occurred: four in the non-treatment year and three in the following treatment years. The overall increase in both lumbar spine and total body bone mineral density were not thought to be associated with an increase in body (bone) size and pubertal development, as most participants were prepubertal.

Weight-bearing exercise

Six participants with DMD (median age: 6.8 years) walking without assistance and taking corticosteroids had whole-body vibration therapy two or three times a week for 10 weeks and were assessed for one year (Söderpalm 2013). No significant changes occurred in bone mineral density in total body, spine, hip, or heel bone or bone markers after the intervention treatment period. No fractures occurred before or during the study. This was a very small observational study with no controls; hence, we could draw no clinical conclusions.

Overall completeness and applicability of evidence

Limited reports from two small studies are only available in published conference proceedings at this time. There is as yet no fully published evidence from randomised trials.

Vitamin D, calcium, and testosterone

We identified no randomised or controlled trials to assess vitamin D, calcium, and testosterone treatment for corticosteroid-induced osteoporosis and fragility fractures in DMD.

Quality of the evidence

We cannot fully assess the quality of the studies from the abstract publications. The two included studies met prespecified eligibility criteria and had small sample sizes ($N = 13$ and $N = 21$). Both trials reported that they randomised participants to an intervention group or no intervention or placebo group. The low-magnitude, high-frequency vibration study reported blinding (Bianchi 2013), but this was unclear in the bisphosphonate study (McSweeney 2014). From the McSweeney 2014 abstract, it was unclear if participants in the intervention group were taking corticosteroids or not.

Of the excluded studies, four were retrospective cohort studies or uncontrolled studies with a small sample size (Biggar 2004; Cohran 2008; Hawker 2005; Srinivasan 2016). These studies had many limitations and provided very low quality evidence.

Potential biases in the review process

There were few limitations to this process. The small randomised controlled trials performed in DMD are unlikely to capture and provide high-quality adverse event data, especially for rare events. The comprehensive searches were updated throughout the review process when necessary.

Agreements and disagreements with other studies or reviews

We examined published systematic reviews that analysed interventions to prevent corticosteroid-induced osteoporosis and fragility fractures in other conditions.

Bisphosphonates

Reviews of treatments for corticosteroid-induced osteoporosis in cystic fibrosis, neuromuscular disease, and chronic illnesses found extensive variation in the choice of bisphosphonate, dosing regimen, and outcome measurement (Conwell 2014; Ward 2007b). Bisphosphonates had a positive effect on the lumbar spine bone mineral density, especially in the short term, although there was some heterogeneity.

The trials reviewed, Conwell 2014 and Ward 2011, reported no new fractures in treatment groups over a two-year period.

In Ward 2007b, although bisphosphonates were well tolerated, the major complaint was bone pain in those taking bisphosphonates but not taking corticosteroids (odds ratio (OR) 18.52, 95% confidence interval (CI) 5.39 to 63.57, six trials). This effect was mostly related to intravenous bisphosphonates (OR 14.17, 95% CI 3.64 to 55.17) and oral risedronate (OR 43.59, 95% CI 2.27 to 837.56). Conwell 2014 listed gastrointestinal effects as a major side-effect.

Overall, both reviews found insufficient evidence to justify the routine use of the bisphosphonates in clinical care to prevent or treat corticosteroid-induced osteoporosis and fractures (Conwell 2014; Ward 2007b). The included trials were too short to monitor vertebral fracture events and treatment adequately.

Vitamin D

Participants with cystic fibrosis taking vitamin D supplements had significantly higher serum levels (mean difference (MD) 7.24 ng/ml, 95% confidence interval 5.01 to 9.46 ng/ml) than those taking a placebo (Ferguson 2014). Vitamin D supplementation was found not to improve bone density in healthy children with normal vitamin D levels, but was found to be clinically useful in children with low serum vitamin D levels by preventing bone loss at the lumbar spine (Homik 1998; Winzenberg 2010).

The vitamin D Individual Patient Analysis of Randomized Trials showed that vitamin D given alone was not effective in preventing fractures (risk ratio (RR) 0.92, 95% CI 0.86 to 0.99, $P = 0.025$), but if taken with calcium, the combination reduced the risk of vertebral fragility fractures (DIPART 2010). Evidence from randomised and cross-over design trials and meta-analysis supports the use of calcium in combination with vitamin D as a preventive treatment for bone loss in the spine of people treated with corticosteroids and adults over 50 years of age (Amin 1999; Homik 1998; Rianthavorn 2012; Tang 2007; Warady 1994). Further research is required to investigate the effect of vitamin D levels on bone strength of patients with DMD (Wong 2010).

Weight-bearing exercise

No useful data were available from studies of weight-bearing exercise in people over 40 with vertebral fragility fractures (Papaioannou 2003). A systematic review of vibration treatment for osteoporosis is published only as a protocol (Lorenzen 2010).

AUTHORS' CONCLUSIONS

Implications for practice

We know of no evidence from high-quality randomised controlled trials (RCTs) about the efficacy of interventions to prevent or treat corticosteroid-induced osteoporosis and prevent osteoporotic fragility fractures in DMD in children and adults, other than limited results from two trials reported in abstracts. There is no evidence of harm, but formal trial reports are awaited. Findings from two ongoing relevant studies and the two trials for which only abstracts are available will be important in future updates of this review.

Implications for research

There is a need for good-quality RCTs of treatments for bone protection and treatment of corticosteroid-induced osteoporosis in Duchenne muscular dystrophy (DMD).

When fully published, the included and ongoing studies of bisphosphonates and weight-bearing activity will be important contributors to this review. Nevertheless, future RCT design and delivery needs to ensure the following:

- employment of an adequate sample size;
- that the clinical indications for starting interventions are addressed;
- that dose, duration, and type of intervention (treatment strategies) are addressed;
- employment of outcomes in addition to bone density Z-scores relevant to children or adolescents, including the number of vertebral fractures, with a clear definition of type of fracture. Pain and quality of life should be also assessed during the trial period and measured using validated scales; and
- assessment of children, adolescents, and adults with DMD or those who are ambulant and non-ambulant separately, as appropriate.

In this group of patients it may not be ethical to withhold treatment or give a placebo, so comparisons could be made to routine care, alternative interventions, or between different treatment groups. It is important that the RCTs consider that age, weight, duration of corticosteroid therapy, mobility, weight-bearing activity, delayed puberty, and growth therapy will affect the outcome measures. Patient groups (children, adolescents, and adults) could be either assessed in separately designed trials, or results could be analysed separately per group to reflect these factors.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bianchi 2013

Methods	Prospective, double-blind, randomised, placebo-controlled study
Participants	Ambulant children with DMD (N = 21) (mean age: 9.3 ± 3.9 years)
Interventions	For at least 6 months before the study, all children were treated with corticosteroids and calcifediol (0.7 mcg/kg/day) and took 100% of the calcium recommended daily allowance Randomised intervention: weight-bearing activity (low-magnitude high-frequency vibration (delivering 0.3 g, 30 Hz; N = 11)) or placebo devices (N = 10) for 10 minutes per day for 1 year
Outcomes	<ul style="list-style-type: none"> Bone mineral density (by dual-energy X-ray absorptiometry) at spine, hip, and total body less head Laboratory tests: calcium, 25-hydroxyvitamin D, and bone turnover markers
Funding sources	Not stated - the abstract did not provide information on funding sources
Declarations of interest	Not stated
Notes	The full trial is not yet published. The conference abstract was published in 2013, but a trial start date and end date has not been provided. An email response from Bianchi 2013 confirmed that there was as yet no more published information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	This was a prospective, double-blind, randomised, placebo-controlled study
Allocation concealment (selection bias)	Unclear risk	The study was reported as an abstract only.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was a double-blind, randomised, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This was a double-blind, randomised, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study was reported as an abstract only.

Bianchi 2013 (Continued)

Selective reporting (reporting bias)	Unclear risk	The study was reported as an abstract only.
Other bias	Unclear risk	The study was reported as an abstract only.

McSweeney 2014

Methods	Randomised controlled trial
Participants	Boys (N = 13) affected with DMD (median age (years): 8.5, range: 5.4 to 15.5) and spine Z-score ≤ 1.0
Interventions	Risedronate group: risedronate 1 mg/kg per week (maximum 35 mg), calcium (500 mg/day), and vitamin D (10 mg/day) (N = 6) Control group: calcium and vitamin D (N = 7) 9 participants were ambulant and on corticosteroid therapy. The effects were determined after 1 year of treatment with risedronate. There was not enough detail in the abstract on timing of risedronate treatment with reference to taking steroids
Outcomes	<ul style="list-style-type: none"> Effects on bone mineral density Z-score
Funding sources	Not stated - the abstract did not provide information on funding sources
Declarations of interest	Not stated
Notes	The full trial is not published. A conference abstract was published in 2014. The trial start date was 22 June 2010 with no end date provided. EudraCT Number: 2009-017649-67

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants (spine Z-score less than -1.0) were randomised to each treatment arm
Allocation concealment (selection bias)	Unclear risk	The study was reported as an abstract only.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was reported as an abstract only.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was reported as an abstract only.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study was reported as an abstract only.

McSweeney 2014 (Continued)

Selective reporting (reporting bias)	Unclear risk	The study was reported as an abstract only.
Other bias	Unclear risk	The study was reported as an abstract only.

DMD: Duchenne muscular dystrophy.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adachi 2001	This study did not include participants with DMD.
Bianchi 2011	This study was not a RCT.
Biggar 2004	This study was not a RCT. The author confirmed this.
Cohran 2008	This study was not a RCT.
Cohran 2013	This study did not include participants with DMD.
Dubowitz 1984	This controlled study did not assess the effect of exercise on bone health
Hawker 2005	This study was a before and after trial, not a RCT.
Houston 2014	This was a retrospective cohort study, not a RCT.
Mayo 2012	This was a prospective observational study, not a RCT.
Sbrocchi 2012	This study was not a RCT.
Scott 1981	This controlled study did not assess the effect of exercise on bone health
Srinivasan 2016	This was a retrospective cohort study, not a RCT.
Söderpalm 2013	This study was not a RCT.
Yilmaz 2004	This study did not assess the effect of the intervention on bone health

DMD: Duchenne muscular dystrophy.

RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

[ACTRN12610000507088](#)

Trial name or title	Clinical trial of zoledronic acid in children and adolescents with Duchenne muscular dystrophy
Methods	Open-label RCT
Participants	Children and adolescents with DMD
Interventions	Zoledronic acid (Aclasta) versus vitamin D plus calcium
Outcomes	<ul style="list-style-type: none"> Change in lumbar spine bone density over 12 months
Starting date	1 September 2010 for the 1st recruited participant
Contact information	email: margaret.zacharin@rch.org.au
Notes	<p>The trial start date was 13 September 2013, and the estimated final collection date was 31 December 2015.</p> <p>Trial ID number: ACTRN12610000507088</p> <p>No further information was published.</p> <p>Source of monetary support: Altum Novartis</p>

[NCT01954940](#)

Trial name or title	Whole body vibration therapy in boys with Duchenne muscular dystrophy
Methods	RCT, parallel assignment, open-label interventional
Participants	Boys with DMD
Interventions	Whole-body vibration therapy
Outcomes	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> Safety of whole-body vibration therapy Gain in muscle strength and prolongation of ambulation from baseline to 8 weeks of therapy <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> A change in muscle strength Any muscle function change Any measurable change in muscle endurance Quality of life changes Gait changes Bone health
Starting date	March 2014
Contact information	Hugh McMillan, MD hmcmillan@cheo.on.ca

NCT01954940 (Continued)

Notes	The trial start date was stated as 13 September 2013, with an estimated final collection date of March 2015. Trial ID number: NCT01954940 No further information, including details of funding, was published
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DMD: Duchenne muscular dystrophy.
RCT: randomised controlled trial.

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Spine and whole-body Z-scores (McSweeney 2014)

	Risedronate (plus calcium and vitamin D supplementation)		Control (calcium and vitamin D supplementation alone)	
	Baseline	12-month	Baseline	12 months
Median spine Z-score (range)	-1.75 (-1.2 to -3.5)	-0.8 (-1.7 to 0)	-2.2 (-4.1 to -1.2)	-1.6 (-8.4 to -0.8)
Median whole-body Z-score (range)	-1.95 (-0.5 to 2.7)*	1.3 (-1.0 to 2.5)	-1.2 (-1.6 to 4.7)	-0.8 (-3.1 to 3)

A median of -1.95 is outside the range given, but we were unable to confirm correct figures with the study author.

APPENDICES

Appendix I. Cochrane Neuromuscular Specialised Register (CRS) search strategy

- #1 muscular NEAR5 dystroph* [REFERENCE] [STANDARD]
- #2 duchenne or dystrophinopathy [REFERENCE] [STANDARD]
- #3 nonambula* or "non ambula*" [REFERENCE] [STANDARD]
- #4 #1 or #2 or #3 [REFERENCE] [STANDARD]
- #5 "vertebral deformity" or fracture or compression or crush or wedging or biconcavity [REFERENCE] [STANDARD]
- #6 osteoporosis [REFERENCE] [STANDARD]
- #7 bone or bmc [REFERENCE] [STANDARD]
- #8 (bone or bmc):so [REFERENCE] [STANDARD]
- #9 #7 not #8 [REFERENCE] [STANDARD]
- #10 lumbar or spine [REFERENCE] [STANDARD]
- #11 MeSH DESCRIPTOR Diphosphonates Explode All [REFERENCE] [STANDARD]
- #12 bisphosphonate* or diphosphonate* [REFERENCE] [STANDARD]
- #13 alendronate or clodronate or etidronate or ibandronate or incadronate or opadronate or pamidronate or risedronate or tiludronate or zoledronate [REFERENCE] [STANDARD]
- #14 calcitonin or calcium or calcitriol or cholecalciferol* or Ergocalciferol* [REFERENCE] [STANDARD]
- #15 "vitamin D" [REFERENCE] [STANDARD]
- #16 "dietary supplements" or testosterone [REFERENCE] [STANDARD]
- #17 Teriparatide or "weight bearing" or diet or exercise [REFERENCE] [STANDARD]
- #18 "non drug" NEXT therapy [REFERENCE] [STANDARD]
- #19 #5 or #6 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 [REFERENCE] [STANDARD]
- #20 #4 and #19 [REFERENCE] [STANDARD]

#21 (#4 and #19) AND (INREGISTER) [REFERENCE] [STANDARD]

Appendix 2. CENTRAL search strategy

Search run on Mon Sep 12 2016

#1(muscular near dystrophy or duchenne near dystrophy or dystrophinopathy or non next ambula* or nonambula*):TI,AB,KY520
#2(“vertebral deformity” or fracture or compression or crush or wedging or biconcavity):TI,AB,KY11862
#3(steroid near1 induced and osteoporosis):TI,AB,KY34
#4(steroid near1 induced and “bone loss”):TI,AB,KY18
#5(steroid near1 induced and osteopenia):TI,AB,KY6
#6MESH DESCRIPTOR Osteoporosis WITH QUALIFIERS CI205
#7(secondary next osteoporosis):TI,AB,KY41
#8(bone next strength):TI,AB,KY248
#9(bone next fragil*):TI,AB,KY51
#10(bone next loss):TI,AB,KY2938
#11(“bone density” or “bone mineral density” or “bone mineral content” or bmc):TI,AB,KY7029
#12(bone next deformity or lumbar next spine):TI,AB,KY3340
#13MESH DESCRIPTOR Spine EXPLODE ALL TREES3740
#14MESH DESCRIPTOR Diphosphonates EXPLODE ALL TREES2659
#15(bisphosphonate* or diphosphonate*):TI,AB,KY1765
#16(alendronate or clodronate or etidronate or ibandronate or incadronate or opadronate or pamidronate or risedronate or tiludronate or zoledronate):TI,AB,KY2255
#17(calcitonin or calcium or calcitriol or ergocalciferol* or “vitamin D”):TI,AB,KY23566
#18MESH DESCRIPTOR Calcifediol EXPLODE ALL TREES215
#19(“dietary supplements” or teriparatide):TI,AB,KY7410
#20(“non drug” next therapy):TI,AB,KY16
#21(diet or exercise or “weight bearing” or testosterone):TI,AB,KY79090
#22#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21119677
#23#1 and #22119
#24sr-neuromusc:cc5974
#25#23 not #2478

Appendix 3. MEDLINE (OvidSP) search strategy

Ovid MEDLINE(R) 1946 to August Week 5 2016

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 randomized controlled trial.pt. (430785)
2 controlled clinical trial.pt. (91698)
3 randomized.ab. (370085)
4 placebo.ab. (178870)
5 drug therapy.fs. (1906928)
6 randomly.ab. (263462)
7 trial.ab. (384951)
8 groups.ab. (1638648)
9 or/1-8 (3900462)
10 exp animals/ not humans.sh. (4315089)

Interventions to prevent and treat corticosteroid-induced osteoporosis and prevent osteoporotic fractures in Duchenne muscular dystrophy (Review)

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11 9 not 10 (3364542)
 12 exp muscular dystrophy/ (23751)
 13 ((muscular adj5 dystrophy) or duchenne or dystrophinopathy).tw. (19784)
 14 (non ambula* or nonambula*).mp. (1602)
 15 or/12-14 (30865)
 16 (vertebral deformity or fracture or compression or crush or wedging or biconcavity).mp. (270009)
 17 ((steroid adj1 induced) and osteoporosis).tw. (252)
 18 ((steroid adj1 induced) and bone loss).tw. (75)
 19 ((steroid adj1 induced) and osteopenia).tw. (37)
 20 osteoporosis/ci (2760)
 21 secondary osteoporosis.tw. (744)
 22 (bone adj1 strength).tw. (4188)
 23 (bone adj1 fragil\$).tw. (1680)
 24 (bone adj1 loss).tw. (23360)
 25 (bone mineral density or bone mineral content or bmc).mp. (38924)
 26 Bone Density/ (45641)
 27 (bone adj1 deformity).tw. (313)
 28 (lumbar adj1 spine).tw. (24195)
 29 Lumbar Vertebrae/ (44335)
 30 exp Spine/ (125272)
 31 exp Diphosphonates/ (22891)
 32 (bisphosphonate\$ or diphosphonate\$).tw. (17118)
 33 (alendronate or clodronate or etidronate or ibandronate or incadronate or opadronate or pamidronate or risedronate or tiludronate or zoledronate).tw. (9832)
 34 Calcitonin/ (14866)
 35 calcium/ (253994)
 36 Calcitriol/ (13310)
 37 exp Cholecalciferol/ (24172)
 38 Ergocalciferols/ (2943)
 39 Vitamin D/ (27463)
 40 Dietary Supplements/ (41269)
 41 Teriparatide/ (1589)
 42 Weight-Bearing/ (17139)
 43 (non-drug adj1 therapy).tw. (103)
 44 (diet or exercise).tw. (454348)
 45 exp Testosterone/ (65868)
 46 testosterone.mp. (91168)
 47 or/16-46 (1299956)
 48 11 and 15 and 47 (319)
 49 remove duplicates from 48 (303)

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1980 to 2016 Week 37>

Search Strategy:

1 crossover-procedure.sh. (48595)
 2 double-blind procedure.sh. (131481)
 3 single-blind procedure.sh. (23071)
 4 randomized controlled trial.sh. (416900)
 5 (random\$ or crossover\$ or cross over\$ or placebo\$ or (doubl\$ adj blind\$) or allocat\$).tw,ot. (1294764)
 6 trial.ti. (207191)

7 or/1-6 (1447525)
 8 exp animal/ or exp invertebrate/ or animal.hw. or non human/ or nonhuman/ (23158822)
 9 human/ or human cell/ or human tissue/ or normal human/ (17529785)
 10 8 not 9 (5661779)
 11 7 not 10 (1276235)
 12 limit 11 to embase (1041572)
 13 exp muscular dystrophy/ (36206)
 14 ((muscular adj5 dystrophy) or duchenne or dystrophinopathy).tw. (23473)
 15 (non ambula* or nonambula*).mp. (2209)
 16 or/13-15 (41054)
 17 vertebra malformation/ (2625)
 18 (vertebral deformity or fracture or compression or crush or wedging or biconcavity).mp. (420882)
 19 corticosteroid induced osteoporosis/ (1750)
 20 ((steroid adj1 induced) and osteoporosis).tw. (356)
 21 ((steroid adj1 induced) and bone loss).tw. (104)
 22 ((steroid adj1 induced) and osteopenia).tw. (52)
 23 osteoporosis/pc [Prevention] (9654)
 24 secondary osteoporosis.tw. (1320)
 25 (bone adj1 strength).tw. (5666)
 26 (bone adj1 fragil\$).tw. (2437)
 27 (bone adj1 loss).tw. (27779)
 28 (bone mineral density or bone mineral content or bmc).mp. (52199)
 29 bone density/ (70004)
 30 bone malformation/ (4902)
 31 (((bone adj1 density) or bone) adj1 deformity).tw. (404)
 32 exp spine/ (149050)
 33 (lumbar vertebra\$ or lumbar spine).tw. (39235)
 34 bisphosphonic acid derivative/ (28745)
 35 (bisphosphonate\$ or diphosphonate\$).tw. (23178)
 36 (alendronate or clodronate or etidronate or ibandronate or incadronate or opadronate or pamidronate or risedronate or tiludronate or zoledronate).tw. (13945)
 37 calcitonin/ (21362)
 38 calcium/ (242503)
 39 calcitriol/ (25813)
 40 colecalciferol/ (14523)
 41 ergocalciferol/ (6751)
 42 vitamin D/ (59328)
 43 diet supplementation/ (75411)
 44 "parathyroid hormone[1-34]"/ (5412)
 45 resistance training/ (9634)
 46 weight bearing.mp. (29389)
 47 (non-drug adj1 therapy).tw. (166)
 48 (diet or exercise).tw. (550445)
 49 testosterone.mp. (114818)
 50 or/17-49 (1607048)
 51 12 and 16 and 50 (162)
 52 remove duplicates from 51 (159)

Appendix 5. CINAHL Plus (EBSCOhost) search strategy

Monday, September 12, 2016 9:27:36 AM

S48 S46 AND S47 5
S47 EM 20150601- 413,167
S46 s45 Limiters - Exclude MEDLINE records
Search modes - Boolean/Phrase 22
S45 S18 AND S19 AND S44 199
S44 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37
or S38 or S39 or S40 or S41 or S42 or S43 334,135
S43 diet or exercise or testosterone replacement therapy 197,974
S42 “non drug” W1 therapy 37
S41 weight W1 bearing 6,645
S40 teriparatide 392
S39 vitamin W1 D 15,233
S38 Cholecalciferol* or Ergocalciferol* 886
S37 calcitonin or calcium or calcitriol 29,703
S36 alendronate or clodronate or etidronate or ibandronate or incadronate or opadronate or pamidronate or risedronate or tiludronate
or zoledronate 2,128
S35 bisphosphonate* or diphosphonate* 6,770
S34 (MH “Diphosphonates+”) 6,762
S33 spine 24,224
S32 lumbar N4 vertebrae 10,854
S31 bone N4 deformity OR lumbar spine 4,994
S30 bone density 14,412
S29 bone mineral density or bone mineral content or bmc 6,242
S28 bone loss 4,602
S27 bone fragil* 260
S26 bone strength 1,008
S25 secondary osteoporosis 203
S24 (MH “Osteoporosis/CI”) 576
S23 steroid W1 induced AND osteopenia 2
S22 steroid W1 induced AND bone loss 8
S21 steroid W1 induced AND osteoporosis 32
S20 vertebral W1 deformity OR (fracture or compression or crush or wedging or biconcavity) 67,110
S19 muscular W5 dystrophy OR (duchenne or dystrophinopathy or “non ambula*” or nonambula*) 3,104
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 855,321
S17 ABAB design* 92
S16 TI random* or AB random* 178,868
S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial
or sham? or dummy)) 355,248
S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or
experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*)) 129,453
S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*)) 48,376
S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind*
or mask*)) 27,566
S11 PT (“clinical trial” or “systematic review”) 131,822
S10 (MH “Factorial Design”) 977
S9 (MH “Concurrent Prospective Studies”) or (MH “Prospective Studies”) 288,464
S8 (MH “Meta Analysis”) 25,156
S7 (MH “Solomon Four-Group Design”) or (MH “Static Group Comparison”) 49
S6 (MH “Quasi-Experimental Studies”) 7,981

S5 (MH "Placebos") 9,796
 S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies") 33,944
 S3 (MH "Clinical Trials+") 202,467
 S2 (MH "Crossover Design") 13,928
 S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample") 73,492

Appendix 6. Web of Science Core Collection - Indexes=CPCI-S Timespan=1900-2016

2001-2016

#19 #17 AND #16

Refined by: DOCUMENT TYPES: (PROCEEDINGS PAPER OR MEETING ABSTRACT)

DocType=All document types; Language=All languages;

#18 #17 AND #16

#17 TS=(random* or "clinical trial" or group or groups or blind* or crossover or "crossover" or "controlled trial")

#16 #15 AND #1

#15 #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2

#14 TS=(bisphosphonate* or diphosphonate* or alendronate or clodronate or etidronate or ibandronate or incadronate or opadronate or pamidronate or risedronate or tiludronate or zoledronate or calcitonin or calcium or calcitriol or cholecalciferol* or Ergocalciferol* or "vitamin D" or "dietary supplements" or Teriparatide or "weight bearing" or diet or exercise or ("non drug" NEAR therapy) or bone or testosterone)

#13 TS=((bone NEAR/3 deformity) or (lumbar NEAR/3 spine))

#12 TS=("bone density" or "lumbar vertebra*")

#11 TS=("bone mineral density" or "bone mineral content" or bmc)

#10 TS=("bone loss")

#9 TS=(bond NEAR/3 fragil*)

#8 TS=(bone NEAR/3 strength)

#7 ts=("secondary osteoporosis")

#6 TS=(induced and osteopenia)

#5 TS=(induced and "bone loss")

#4 TS=(induced and osteoporosis)

#3 TOPIC: (fracture or compression or crush or wedging or biconcavity or lumbar or spine)

#2 TOPIC: ("vertebral deformity" or fracture or compression or crush or wedging or biconcavity or "vertebral deformity")

#1 TOPIC: ((muscular NEAR/5 dystroph*) or duchenne or dystrophopathy or nonambula* or "non ambula*")

Appendix 7. clinicaltrials.gov search strategy

Search performed 11 October 2016

Duchenne muscular dystrophy AND (bone OR bone mineral density OR fractures) AND (vitamin D OR calcium OR testosterone OR physical activity OR exercise)

Appendix 8. apps.who.int/trialsearch/ search strategy

Search performed 11 October 2016.

The following terms were used:

Duchenne muscular dystrophy AND bone 8

Duchenne muscular dystrophy AND osteoporosis 1

Duchenne muscular dystrophy AND bisphosphonates 1

Duchenne muscular dystrophy AND vitamin D 2

Duchenne muscular dystrophy AND calcium 3

Duchenne muscular dystrophy AND testosterone 1

Duchenne muscular dystrophy AND whole body vibration 1

Appendix 9. www.isrctn.com search strategy

Search performed 11 October 2016

Duchenne muscular dystrophy

Appendix 10. Additional methods described in the protocol

Data extraction and management

Two review authors (JMB and MS) will independently extract data using a standard data extraction form. One author (JMB) will enter data into the Cochrane software Review Manager 5 (RevMan) ([RevMan 2014](#)), and a second author (MS) will check data entry. JMB will contact study authors directly for any additional or missing data required. We will note in the 'Characteristics of included studies' table if outcome data are not reported in a usable way.

Where studies provide data on our outcomes at time points less than or more than 24 months, we will extrapolate the data to 24 months when it is reasonable to do so. We will assume a linear response rate but carry out a sensitivity analysis to assess the effects of the imputation, by re-analysis using alternative imputed values.

Measures of treatment effect

Statistical methods used to measure treatment effects will be in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)).

We will analyse dichotomous data as risk ratios (RR) and continuous data as mean difference, or standardised mean difference for results across studies with outcomes that are conceptually the same but measured in different ways. We will report these measures of effect with 95% confidence intervals (CI).

We will undertake meta-analyses, using RevMan, only where this is meaningful, that is, if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

Unit of analysis issues

Where a single trial includes multiple trial arms, we will include only the relevant arms. If we combine two comparisons (e.g. drug A versus placebo and drug B versus placebo) in the same meta-analysis, we will halve the control group to avoid double-counting. For each participant, there may be multiple observations for the same outcome.

Dealing with missing data

We will attempt to contact the trial correspondence author to obtain any missing data. If we are unable to obtain data, we will try to find out why the data are missing and decide, based on whether they are missing at random or not, whether to analyse available data or impute missing values using a statistical model. We will consider how best to include missing data where baseline-observation-carried-forward (BOCF) or last-observation-carried-forward (LOCF) methods have been used for imputation and attempt to standardise these between studies (LOCF being preferable).

We will address the potential implications of missing data (for example, loss to follow-up and no outcome obtained, lack of compliance) in the 'Discussion'.

Assessment of heterogeneity

We will assess clinical heterogeneity by judging, qualitatively, the differences between studies regarding the participants, therapies, and reporting of important study outcomes.

We will statistically test heterogeneity of intervention effects among trials using the standard χ^2 statistic (P value) and the Higgins I^2 statistic expressed as a percentage. We will take P values of less than 0.05 as evidence of heterogeneity. We will interpret I^2 for heterogeneity as follows:

- 0% to 40%: may not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

If we identify substantial unexplained heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis ([Higgins 2011b](#)).

Assessment of reporting biases

To detect the presence of publication bias, we will construct a funnel plot using RevMan if there are a reasonable number of studies (at least 10 in the same meta-analysis). We will use Beggs's and Egger's tests to verify the bias ([Begg 1994](#); [Egger 1997](#)).

Data synthesis

If there is no substantial or considerable heterogeneity, we will synthesise the data in a meta-analysis using RevMan. We will perform both fixed-effect and random-effects models for comparison purposes and use the most appropriate, depending upon the degree of heterogeneity.

If the review includes more than one comparison, and we cannot include them in the same analysis, we will report the results for each comparison separately.

Cost-utility analyses

We will consider cost-effectiveness of interventions per QALY (quality-adjusted-life-year) in the Discussion, where data are available.

Subgroup analysis and investigation of heterogeneity

If there are sufficient data, we plan to undertake the following subgroup analyses using the outcome vertebral fractures:

1. ambulant versus non-ambulant (due to disease progression, these groups will reflect age groups); and
2. intervention versus intervention combination.

Within each group, we will use the I^2 statistic for heterogeneity, and if its value is greater than 50%, we will scrutinise the trials and forest plots for differences to explain the heterogeneity. If we find no explanation, we will repeat the analysis using a random-effects model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes:

- change in bone mineral density as assessed by Z-score;
- frequency of vertebral fragility fractures; and
- adverse events.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions*, [Higgins](#)

2011a, using GRADEpro software. We will justify all decisions to downgrade or upgrade the quality of studies using footnotes, and we will make comments to aid readers' understanding of the review where necessary.

Sensitivity analysis

We will perform a sensitivity analysis to determine whether conclusions are robust by undertaking both fixed-effect and random-effects meta-analysis. We will perform sensitivity analyses to assess the effect of including studies at high risk of bias on the change in vertebral bone mineral density (body height corrected Z-scores), and by repeating the meta-analysis excluding any studies at high risk of bias. If we have imputed missing data, we will assess the effects of the imputation by re-analysis using several alternative imputed values.

CONTRIBUTIONS OF AUTHORS

Jennifer Bell prepared the protocol with discussion and comments from review authors. Dr Janet Watters reviewed the text from the perspective of a healthcare consumer as the mother of a boy with Duchenne muscular dystrophy.

Conceiving the review: MS; BB

Co-ordinating the review: JMB

Undertaking manual searches: JMB

Organising retrieval of papers: JMB

Screening retrieved papers against inclusion criteria: JMB; MS

Writing to authors of papers for additional information: JMB

Data management for the review: JMB

Data extraction and quality assessment: JMB; MS

Interpretation of data: JMB; MS; BB

Writing the review: JMB with contributions from all authors

Guarantor for the review (one author): MS

Person responsible for reading and checking the review before submission: JMB and all authors

DECLARATIONS OF INTEREST

JMB: none known

TB: acknowledges financial support received from Servier Laboratories Ltd and Amgen UK Ltd to attend national conferences and payment with respect to chairman and speakers fees.

BB: none known

ME: none known

AH: none known

RQ: is Joint Co-ordinating Editor of Cochrane Neuromuscular and is the author of two consensus workshop reports for bone health in Duchenne muscular dystrophy. Dr Quinlivan has received an honorarium from Genzyme for lecturing on metabolic muscle disease, as well as consultancy fees from Novartis and Guidepoint Global.

MDS: has received honoraria from GlaxoSmithKline, AstraZeneca, Novartis, Merck Sharp & Dohme, and ALK-Abelló for lectures given at educational meetings and received hospitality to attend the European Respiratory Society and British Thoracic Society annual meetings.

ST: none known

JW: a member of charities Action Duchenne and the Muscular Dystrophy UK.

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Internal sources

- No sources of support supplied

External sources

- Health Research Board/HSC R&D Division Cochrane Fellowship Award, Ireland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Lack of data prevented full implementation of our protocol ([Bell 2014](#)).